Yohimbe Bark

Its History and Identification in Commerce

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BY

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So-called yohimbe bark is obtained from various species of trees or shrubs belonging to the family Rubiaceæ, which grow in the southern district of the Cameroons, Nigeria, the French Congo, Golungo Alto in Angola, Oban in Nigeria, and the Gaboon.

The genuine bark yields several alkaloids, the most important one being known as yohimbine or corynine. The first use of this alkaloid as a drug is comparatively recent, and the active alkaloid is found in much larger proportions in certain species. One species, *Pausinystalia macroceras*, known as false yohimbe bark, yields mainly the inactive alkaloid yohimbenine, therefore it is of importance to be able to identify these barks in commerce.

History.

Nothing is recorded concerning yohimbe bark before 1896, so its history may be said to date from that time, when it was investigated chemically and therapeutically to a certain degree by Spiegel[24], who patented the active principle in Berlin as yohimbine.

Present Position in Medicine.—The use of yohimbe bark in ordinary medical practice has been known since 1900, when it was investigated by Oberworth and Loewy[18] [33], who found it to be in animals, and also in man, an active aphrodisiac. Another investigator, Krakoff[15], is said to have concluded, as the results of experiments on the lower animals and on man, that the drug had no aphrodisiac effects, and that, on the other hand, it frequently caused salivation, nausea, irritability, and other disagreeable symptoms. It has been used by numerous clinicians in neurasthenic impotence, with reports generally favourable to its influence. It is said to be of no value when the impotence depends upon organic nerve trouble, and to be harmful when it is caused by chronic inflammatory disease of the sexual organs. The dose given of yohimbine hydrochloride is usually ·005 Gm. Yohimbine has also been employed hypodermically in a 10 per cent. solution.

In the 1911 edition of the British Pharmaceutical Codex the botanical source of yohimbe bark is still given as *Corynanthe Yohimbe*. According to that work, the alkaloid is known also under the name corynine, as well as the trade names of yohimbine and aphrodine. The 1915 Supplement of the B.P. Codex gives Yohydrol as the trade name of yohimbine hydrochloride. The melting-point of yohimbenine is given as 105° to 106° C.

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The process of extraction described in the German patent is also given as follows:—"The powdered bark is exhausted with diluted acetic acid, and the alkaloid is precipitated by means of sodium carbonate; the product is then dried and crystallised from alcohol." The B.P.C. also gives the following:—"It is a tertiary base, optically inactive, and has certain properties in common with cocaine, its hydrochloride acting as an anæsthetic when applied to the cornea in solution of $\frac{1}{4}$ per cent. to 1 per cent. strength, the anæsthesia lasting for one hour or more. Its effects are more persistent than those of tropa-cocaine. Yohimbine may be distinguished from cocaine in many ways, the latter being permanent in air and melting at 98° C. Yohimbine is employed hypodermically or by the mouth as a sexual stimulant in impotence; its action as an aphrodisiac is said to be superior to that of strychnine, in that while strychnine increases all reflexes, yohimbine increases only the pelvic reflexes. Yohimbine also exerts an anæsthetic action upon sensory nerve terminations. It lowers blood pressure by dilating the vessels; this action is exerted on the walls of the vessels themselves, and affects most vessels, such as those of the skin, kidneys, intestines, and external genital organs. It increases depth and frequency of respiration. Poisonous doses paralyse respiration. It has been used as a local anæsthetic for the eye in place of cocaine. It produces no mydriasis, and does not affect the corneal epithelium. It is chiefly used in the form of the hydrochloride. The dose is usually 3-8 Mgms. (1-20 to 1-8 grain)."

It is of interest to note that a liquid preparation for veterinary use, sold under the trade name "Yohimbine Schmidt," was shown by Kobert[14] in 1912 to be a preparation of veratrine (cevadine), not of yohimbe bark.

Botanical.—In 1902, Schumann[21] identified the bark as that of *Corynanthe Yohimbe*, from Kribi, in the Cameroons, and distinguished the species from others of the same genus by the winged tails of the corolla lobes. The bark he describes as being from 8-10 Mm. thick, with an external corky layer of a grey-brown colour, covered with isolated lichens, and showing longitudinal and transverse fissures like old cinchona. The transverse fracture he describes as of an uniform yellow-brown colour, with a short, soft fibrous surface like rough velvet. Under the microscope the structure much resembles that of *Cinchona*, but differs in the arrangement of the bast fibres of the secondary bark in definite long radial rows.

In 1904, Herzog[11] examined a substituted false bark, that of *Corynanthe macroceras*, and stated that this bark contains little yohimbine and larger quantities of totally inert alkaloids, which are closely allied to the active yohimbine. This was an important discovery, as this species closely resembles other barks from the same region—*i.e.*, the Cameroons—which yield the drug of medicinal and commercial value. The taxonomic position of this and the species yielding the genuine bark was changed in the following year, and the name *Pausinystalia* replaced *Corynanthe* (in part). This was done by Beille and Dupony.

In 1906, Beille[3], in collaboration with Professor Dupony, made a pharmacological study of a bark said to have aphrodisiac and anæsthetic properties imported from the French Congo, and known to the natives by the name "Eudun." This new species was described as *Pausinystalia Trillesii*, and placed with the other two already known in the new genus *Pausinystalia*.

The two genera *Pausinystalia* and *Corynanthe* are distinguished by Beille and Dupony by the following morphological and anatomical characters:—

Pausinystalia is characterised by its very thick branches, by its almost sessile and whorled leaves, by its rotate or campanulate corolla, with winged lobes, included stamens and style, conical and bi-lobed stigma, and, lastly, by its septicidally dehiscing fruit. Other characters of calyx, ovary, placentation, etc., are to be found also in allied genera—*e.g.*, *Cinchona*.

Corynanthe has branches which are not at all thick, leaves opposite and with long petioles. The blade of the leaf has not the bright tint which is characteristic of *Pausinystalia*. The corolla is funnel-shaped, and has a slender tube as long as the lobes. In *C. paniculata* (Welw.) (= *Pseudo-cinchona africana* (A. Chev.), the appendages or wings are about the same length as the lobes, and in *C. pachyceras* (K. Sch.) they are very short and dilated. The stamens and style are exserted to some distance; the stigma is in the form of an oblong club, and is entire. The capsule has loculicidal dehiscence.

The linear form of the wings of the corolla lobes, their development varying from 11 to 24 Mm., is characteristic of *Pausinystalia*, whilst in *C. paniculata* they are 2 Mm. in length, and in *C. pachyceras* they are scarcely 1 Mm.

Beille[3] gives the following distinctions for the three species of *Pausinystalia*, together with the original diagnosis of *P. Trillesii* as drawn up by Pierre.

P. Yohimba (K. Sch.), Pierre; *Corynanthe Yohimbe* (K. Sch.): Leaves large, corolla campanulate with a short tube, appendages to the corolla lobes 23 Mm. long.

P. macroceras (K. Sch.), Pierre; *Corynanthe macroceras* (K. Sch.). Leaves obovate, broadly obtuse, corolla urceolate with appendages 11-12 Mm. long.

P. Trillesii, Pierre: Leaves obovate and apiculate, the lower part of the leaf becoming rather narrower than the upper part, making the lower third of the leaf blade vaguely oblong, the axillary panicled inflorescence is branched towards the middle, capsule oblong, and attenuated towards the base.

The variation in anatomical structure of the stems is described as follows:—

In *Corynanthe paniculata* the stem shows cortical parenchyma heterogeneous, *i.e.*, radial zones of little cells with thickened walls are separated by zones of larger cells with thin walls. The secondary bast bundles are of triangular shape, in transverse section, with little bundles of 3-5 pericyclic fibres outside; the bast fibres are isolated and not very numerous.

In *P. Yohimba* the stem shows homogeneous cortical parenchyma, *i.e.*, formed of almost regular polygonal cells. The bast bundles are triangular, in transverse section, and have bundles of 5-8 pericyclic fibres outside; the bast fibres are numerous and isolated.

In *P. Trillesii* the stem shows homogeneous cortical parenchyma, formed of less regular cells than in the preceding species. The bast bundles are less thinned off exteriorly, giving a truncate apex to the triangle, and have bundles of 8-12 pericyclic fibres outside; the bast fibres are numerous and isolated.

The constitution of the cortical parenchyma, the development, greater or less, of the pericycle and the bast fibres of the stem, and the development of the bast bundles, are the anatomical characters which can be used to differentiate the genera *Corynanthe* and *Pausinystalia*.

In the same year Beille and Dupony[4] added *P. Trillesii* to those species already known to yield yohimbine. They stated that the alkaloid was identical in all its reactions with yohimbine, but the small amount of material available prevented them

from making an ultimate analysis of the base. This investigation almost seems to have exhausted the available supply of the bark of *P. Trillesii*, since authentic material, even on repeated and extensive inquiry for the last three years, has not been obtainable.

According to Holmes,[13] these three species, *P. Yohimba*, *P. macroceras*, and *P. Trillesii*, possibly enter English or French commerce, since they occur together in the French Congo. The first two also occur in the Cameroons. Several other allied species—*e.g.*, *Corynanthe pachyceras*, from Nigeria and the Cameroons, and *Pausinystalia Talbotii*, from Oban, in Nigeria—are known to occur in British possessions in West Africa. Other known species are *P. Angolensis*, from Golungo Alto, in Angola; *C. paniculata*, also from Angola; *C. Gabonensis*, from the Gaboon; and *C. Lane-Poolei*, from Sierra Leone.

Chemistry.

Formulæ.—Arnold and Behrens,[1] in 1902, gave the formula for yohimbine hydrochloride as $C_{22}H_{28}N_2O_3HCl$. These authors also refer to the recent introduction of yohimbine as an aphrodisiac, and draw attention to the distinctions between yohimbine and cocaine.

Siedler,[22] about the same time, investigated a yohimbe bark said to be obtained from a West African species of *Tabernæmontana*, and found four alkaloids. He also[23] gives the results of further analysis of the alkaloids of yohimbe bark. He separated the so-called yohimbine with the formula $C_{22}H_{30}N_2O_4$, or $C_{23}H_{32}N_2O_4$, into two bases by fractional distillation from benzole, one having a melting-point 231° C., the other with a melting-point 234° C. The melting-point given by Spiegel[24] was 231° C.; that given by Thoms[29] was 234° C.

In 1903 Spiegel,[25] whose name is first connected with the investigation of the alkaloids of yohimbe bark eight years before, gives further notes on the chemical composition of yohimbine. He gives for the anhydride the formula $C_{22}H_{28}N_2O_3$, melting-point 234°-234·5° C., and abandons the name nor-yohimbine in favour of Wurzheim's name, yohimboasic acid, for a derivative $C_{20}H_{26}N_2O_4$, which is a monobasic acid as well as a monoacid base.

The formulæ given by Weigel[30] in 1907 are the same as the two given by Siedler, but Weigel also gives a third, $C_{21}H_{28}N_2O_4$, and points out that one of the others loses water to form the anhydride $C_{22}H_{28}N_2O_3$. The formulæ are, therefore, not established, but Siedler's two and the anhydride formula of Arnold and Behrens are generally accepted.

In 1915 Spiegel[26] separated mesoyohimbine, with melting-point 247° to 248° C., from yohimbine, and gave for the former the formula $C_{21}H_{26}N_2O_3$. In the same year Barger and Field[2] confirmed Spiegel's formula for the anhydrous base, $C_{22}H_{28}N_2O_3$. These authors also state that under a pressure of 8 Mm. the alkaloid sublimes below its melting-point at 210°-220° C., and forms thin needle-shaped crystals, which show a melting-point at 220° C.

Tests and Characteristics.—A considerable amount of chemical investigation of the alkaloids was recorded by several workers in 1907. Weigel[30], still using the name *Corynanthe Yohimbe* for the source of the true bark, adds that another kind of yohimbe bark is obtained from the French Congo, and is known as *Pausinystalia Trillesii*, closely allied, but differing in its histological characters. He also mentions *Corynanthe macroceras* as the source of a third bark, containing chiefly yohim-

benine, which is inactive, and comparatively little yohimbine. He gives tests for the true bark as follows:—A few particles shaken with very dilute caustic soda solution (*i.e.*, 10 drops of a solution of s.g. 1·168 in 30 C.c. water) impart a wine-red colour to the liquid, which becomes deeper on standing. If about 1 Gm. of the powder be shaken with 20 C.c. of 1 per cent. HCl and filtered, the filtrate should give a voluminous white precipitate with Mayer's reagent.

The presence of yohimbine is proved thus:—2-3 Gms. of powdered bark are shaken up with a mixture of 25 C.c. ether, 5 C.c. chloroform, and 2 C.c. ammonium hydroxide solution for fifteen minutes. The ethereal solution is then filtered into a separator and shaken out with 30 C.c. 1 per cent. HCl. The acid liquid is then separated, the dissolved ether is driven off with gentle heat, the alkaloids are precipitated with a slight excess of ammonium hydroxide, collected, and washed with water. If a portion of the precipitate is placed on a watch-glass over a white background and dissolved in 1 C.c. strong sulphuric acid and crystals of potassium bichromate added, a deep bluish-violet colour is produced if the alkaloid is yohimbine. Four alkaloids were found by Spiegel, and Weigel reports the solubilities as follows:—

Yohimbine, sparingly soluble in ether, more soluble in absolute alcohol, readily soluble in chloroform;

Yohimbenine, readily soluble in ether as well as in the other solvents;

An unnamed alkaloid which is sparingly soluble in ether and readily soluble in alcohol and chloroform;

A base which is insoluble in ether and sparingly soluble in alcohol and chloroform.

According to Weigel, yohimbine occurs in the twigs and leaves as well as in the bark, and in addition to the above-mentioned bases a non-alkaloidal constituent which imparts a green fluorescence to chloroform, and a colouring body giving red with alkalies, are also present. The same author states that true yohimbine crystallised from dilute alcohol forms pure white opaque, silky needles, with melting point 213° C., which are soluble in most organic liquids, but are insoluble in benzene. This is characteristic. Exposed to light and air both the base and its salts become yellow. Other characters given by Weigel are: yohimbine is a tertiary base with an aldehydic function, and powerfully reduces ammoniacal silver nitrate. It contains a methoxyl group, and is oxidised by potassium permanganate solution. It gives at least two acids, yohimbinic acid with m.p. at 85° C. and nor-yohimbinic acid. On saponification another acid is formed, *i.e.*, yohimboasic acid, of which yohimbine is a methyl ester. Yohimboasic acid is identical with Spiegel's nor-yohimbine. Weigel also gives several tests by which yohimbine can be distinguished from cocaine.

Reichard[19] gives the following characteristic reactions of yohimbine:—

1. Yohimbine with cold concentrated sulphuric acid gives no colour. If excess of the liquid is removed with filter paper, the moist mass which is left shows a marked light blue fluorescence.

2. When yohimbine hydrochloride is dissolved in hydrochloric acid and warmed, it gives a blue colour which turns greyish-blue on cooling.

3. The salt, yohimbine hydrochloride, gives a yellow colour without dissolving in 25 per cent. nitric acid. On dilution the yellow colour remains. When the yellow mass is warmed the colour partly disappears and the mass becomes a greenish-yellow colour.

4. The salt, when treated with dilute caustic soda, shows under the microscope the characteristic prisms of yohimbine, and with suitable illumination a bluish fluorescence.

5. When yohimbine hydrochloride is rubbed up with crystals of potassium bichromate and a few drops of water added a yellow precipitate of yohimbine bichromate is formed which gradually becomes blue, leaving the edge yellow.

6. Treated in the same way with ammonium molybdate, yohimbine hydrochloride gives a darker blue colour.

7. Yohimbine with potassium ferrocyanide and water gives a bluish zone round the mixture. When this dries it gives rise to a bluish band with a bluish reflection, the inner part is golden, and the colours are discharged by hydrochloric acid.

The tests given in the B.P.C. are similar. Alkalies give an orange-yellow colour with the alkaloid; the sulphuric acid and bichromate test as for strychnine gives streaks with blue-violet edges gradually becoming dirty green. Reichard's second test applied to the alkaloid is said to give an intense yellow instead of a blue colour. A new test is given—the alkaloid dissolved in 50 per cent. sulphuric acid and warmed with a few grains of cane sugar on a water-bath develops a wine-red colour. Yohimbine is described as almost insoluble in water, slightly soluble in ether or benzene, soluble in alcohol, methyl alcohol, acetone, or chloroform.

Several other tests are given by Mellière[16] who remarks upon the fact that yohimbine, unlike most alkaloids, gives colour reactions similar to those of bile acids. The reaction, described above, with sulphuric acid and sugar or with sulphuric acid and furfurol, is similar to Pettenkorfer's reaction for bile acids. Similarly with Marquis's reagent, sulphuric acid and vanillin, it yields a deep permanent carmine. A similar colour is produced with sulphuric acid and a trace of salicylic aldehyde. The acid used for these tests is the usual concentrated acid diluted with water in the proportion of one volume of water to two volumes of acid. This avoids the masking colours which are developed with strong acid if the material is not quite pure.

Estimation of Alkaloids.—Spiegel[24] isolated four distinct alkaloids from yohimbe bark differing in solubility in alcohol, ether, and chloroform, and found the total alkaloids to be 0·3 to 1·5 per cent. Thoms[29] the following year, 1897, confirmed Spiegel's results, obtaining 0·54 per cent. from the leaves as well as from the bark. This author gave 234° C. as the melting-point, while Spiegel gave 231° C. Siedler, as noted above, afterwards separated two bases with these two melting-points, and it would seem that Thoms and Spiegel were dealing with different although closely allied alkaloids. Other melting-points which have been given are 213° C. by Weigel, and 220° C. by Barger and Field.

Although the estimation of the total alkaloids is a fairly easy process, the separation of yohimbine from yohimbenine in practice is very difficult, and according to the chemical experts has not yet been done quantitatively. Last year a method depending upon the greater solubility of yohimbenine in ether was published by Schomer[20], but the process of purification (by washing with ether in which yohimbine is slightly soluble, and by agitation with chloroform in which the crystals are said to float, but in which yohimbine is described by other authors as readily soluble) does not seem to be an altogether satisfactory one from a quantitative point of view. The description of the ultimate product as a *yellowish*-white

powder points to the action of air and light upon the alkaloid during the extraction and separation. This method might, however, be used to check the results of the present investigation, as it is the only one yet published which makes any attempt at quantitative separation of the two chief alkaloids. There is a full description of it in the 'Year-Book of Pharmacy' for 1921.

Yohimbine and Quebrachine.—The action of salts of yohimbine on the heart has been carefully studied by Müller[17], Gunn[10], and Tait[28]. Hesse[12] considered yohimbine to be identical with quebrachine, while Fourneau and Fiore[7] concluded in 1911 that they were optical isomers.

In 1914 Fourneau and Page[8] state that quebrachine, an alkaloid obtained from quebracho bark belonging to the family Apocynaceæ, is identical with yohimbine from the Rubiaceæ, and comment on the rarity of this similarity in alkaloids obtained from such widely-separated families of plants, the only other known instance being that of berberine.

Ewins[5] in 1915 investigated the alkaloids of *Aspidosperma Quebracho*, and states, as the result of his analysis, that the bark yields 0·06 to 0·2 per cent. of aspidospermine or quebrachine He gives the formula $C_{22}H_{30}O_2N_2$, and various chemical data. The formula, it will be seen, is very similar to but not exactly the same as certain of the various formulæ given for yohimbine. It might be mentioned here that the alkaloid aspidospermine, or quebrachine, had already been investigated, and in 1878 was exhibited at the Paris International Exhibition as a valuable drug in the treatment of different lung diseases. Evidently the bark is of a very tough nature, the name quebracho signifying "breaking the axe to pieces."

The 1916 edition of the United States Pharmacopœia[34] gives a fairly full description of *Aspidosperma Quebracho*, from which one can gather that, although the barks have certain similarities, they can be easily distinguished by a macroscopic or microscopic examination.

Barger and Field[2] in 1915 brought forward chemical data suggesting that yohimbine and quebrachine are identical. In the same year this evidence was controverted by Spiegel[27], who maintained that the identity of the two alkaloids was not proved, since their quebrachine preparations had a melting-point from 220°-225° C., which is considerably below the melting-point (234° C.) of pure yohimbine from which meso-yohimbine has been separated.

Filippi[6] in 1917 corroborates Spiegel from pharmacological observations, which show such marked differences between yohimbine and quebrachine that they cannot be considered identical although belonging to the same pharmacological group.

These results were confirmed by Gibson,[9] who compared the action of yohimbine with that of quebrachine. These alkaloids both produce heart-block, but in different ways—yohimbine by acting chiefly on the conducting bundles, and quebrachine mainly by depressing the irritability of the general mass of cardiac musculature. The depressing effect of yohimbine is increased by activity of the muscle. The two kinds of heart-blocking are A.V. blocking (*i.e.*, blocking by indefinite prolongation of the interval between auricular systole and ventricular systole) and S.A. blocking (*i.e.*, blocking between sinus and auricle). Yohimbine perfused generally brings about complete A.V. blocking before there has been any S.A. blocking; with quebrachine this is very rare indeed, S.A. blocking frequently appearing first.

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TABLE OF D

—	*P. Yohimba.*	*P. macroc*
Microscopic Characters		
Thickness	4-20 Mm.	4-15 Mm.
Outer Surface		
Colour	Grey to reddish brown	Light or dark brow
Surface	Longitudinal furrows; many transverse cracks, 1-2Cm. apart	Often scraped; lc and ridges; fe transverse crack
Lichens	Grey or white; few or many	Grey, usually nume
Cork	Thin, adhering closely	Thin or thick, of tachable
Inner Surface		
Colour	Reddish brown	Dark brown or r
Surface	Finely striated and ridged	Ridged and wrinkl
Fracture	Short, fibrous, sometimes splintery on inside, surfaces soft, velvety	As for *P. Yohimba*
Microscopic Characters		
Cork		
Width of Cork	1/20 to 1/3	1/4 to 2/3
Width of Cortex		
No. of cells wide	3-30	2-40
Colour	Grey to dark brown	Dark brown
Phelloderm		
No. of cells wide	2-12	4-20
Colour	Yellowish grey to reddish brown	As for *P. Yohimba*
Cortex		
Width of cortex	1/16 to 1/1	1/6 to 1/1
Width of Bast		
Colour	Yellowish brown to reddish brown	As for *P. Yohimba*
Medullary Rays		
T. S. inner bast Width	1-4 cells	1-3 cells
Regularity	Straight	Straight
T. S. outer bast Width	1-3 cells	1-3 cells
Regularity	Diverging, cells elongate tangentially	Curve irregularl tangentially
Ends	Straight or curved	Often distorted, c
L. S. tangential Width	1-3 cells	1-3 cells
Depth	6-35 cells	5-20 cells
Shape	Narrow spindle or rectangular	Somewhat rect slightly taperin
L. S. radial Depth	8-30 cells	5-20 cells
Bast Fibres		
Grouping	Usually in one-cell wide rows, 1-3 occur, "beaded," no "twinning" in outer bast	Radial rows 2 common, not " "Twinning" in bast
Diameter	22-39 μ	22-33 μ
Length	0·7-1·6 Mm.	0·6-1·9 Mm.
Shape T.S.	Rectangular	Rectangular
L.S.	Long spindle, pointed ends	Spindle, with e ends
Lumen	Punctiform or sometimes linear	Linear, or somet
Wall	Thick, not striated	Thick, not striat

ARACTERS.

C. paniculata.	*C. Lane-Poolei.*
-5 Mm.	2-4 Mm.
Grey to yellowish brown Finely wrinkled and ridged longitudinally	Light yellow brown to darker brown. Longitudinally ridged and cracked; transverse cracks few, ·5-4·0 Cms. apart
Yellow or grey, numerous	Grey or shiny green, numerous
Thin, adheres closely	Thick, easily detachable
Yellowish brown Very finely striated	Light brown Very finely striated
Short externally, splintery internally, surfaces hard and rough	Fibrous or splintery, surfaces rough
—	—
1-10 Dark brown	10-12 Dark brown
4-6 Reddish brown	4-12 Yellowish to reddish brown
Absent in specimens	Absent in specimens
1-3 cells Undulating 1-3 cells Curved, cells elongate tangentially Curved 1-3 cells 9-20 cells Spindle	1-3 cells Straight 1-3 cells Straight, cells elongate tangentially Straight or curved 1-3 cells 9-12 cells Spindle
9-20 cells	9-12 cells
Radial rows, 1-3 cells wide, some "beading"	As for *P. macroceras* With some "beading" and "twinning"
5-22 μ About 1 Mm. Flattened tangentially and contorted.	22-25 μ 0·7-1·2 Mm. Rectangular
Spindle, pointed ends.	Spindle, with sharply pointed ends
Open, nearly linear; collapsed	Linear or punctiform
Thinner, not striated	Thick, not striated

Several other differences in action were observed by Gibson, who concluded that the action of the two alkaloids on the heart is very similar. In small doses quebrachine probably acts as a stimulant to the heart, but with large doses the heart is paralysed, and stops in diastole. In about one-third of the hearts perfused, S.A. blocking appeared before A.V. blocking with quebrachine, while A.V. blocking always occurred before S.A. block with yohimbine.

In 1919 Holmes[13] records some of the various points in the history of the drug as given above. He states that previous to the war yohimbe bark was exported from the Cameroons to Germany. With the war, exportation stopped, and manufacture in Germany ceased, but the trade mark "Yohimbine" was still (1919) on the British register. Then, he continues, it was found that *Pausinystalia Trillesii*, yielding yohimbine, occurred in the French Congo, and the manufacture of the alkaloid was taken up in France, where the demand appeared to be large. We are informed that *P. Trillesii* is known to occur only near Libreville, the capital of the French Congo, and the difficulty in obtaining authentic material has already been mentioned. Yohimbine was said to be used by people who could not get cocaine, and to be certainly used as an aphrodisiac in veterinary practice. Holmes also distinguished the bark of *P. Yohimba* as occurring in thin, hard, slightly curved pieces, about 2-3 Mm. thick, and fibrous; while that of *P. macroceras* is described as usually about 1 Cm. thick, softer and more loosely fibrous; but these diagnostic characters have not been found valid during the present investigation of more extensive material than was then available.

Such is the history of this new drug, the reputation of which has been endangered by the difficulty experienced even amongst experts of distinguishing the true yohimbe bark from the numerous more or less worthless substitutes derived from closely-allied species. Chemical tests have been described by competent analysts as useless; macroscopical and microscopical examinations by other experts have yielded no good diagnostic characters. A thorough comparative investigation of all available material was, therefore, suggested by E. M. Holmes, who has very kindly provided the majority of the samples used in the first stage of the investigation.

Investigation.

A comparative examination has been made of a number of authentic herbarium or museum specimens of various species of *Pausinystalia* (*P. Yohimba*, *P. macroceras*, *P. Talbotii*) and *Corynanthe* (*C. paniculata*. *C. Lane-Poolei*), of certain authentic museum specimens of Yohimbe, of certain doubtfully authenticated specimens, and of eleven commercial samples; appended are the results of a supplementary investigation of seven commercial samples kindly supplied by an importing firm of African merchants, Messrs. W. D. Woodin and Company. The macroscopic and microscopic characters are recorded in some detail in the accompanying schedule, drawn up from the notes on all the specimens of the four chief species:—

Bark of Pausinystalia Yohimba, K.Sch.

Macroscopic Characters.—The two authentic specimens of true yohimbe bark showed the following characters:—Flat or channelled pieces, 4-8 Mm. thick; outer surface dark brown or greyish brown with a tinge of red of varying distinctness; grey encrusting lichens and leafy liverworts in patches; the outer surface wrinkled and ridged longitudinally, with trans-

verse cracks very common 1-2 Cm. apart, giving a general pattern of square cut patches. The cork was thin and adhered closely to the outer layers of the back. The inner surface was reddish, finely striated and ridged longitudinally. The fracture was splintery, giving soft, velvety surfaces.

MICROSCOPIC CHARACTERS.—These were examined in young bark from herbarium specimens as well as in the older specimens. The older barks, Figs. 3-4, show a thin layer of cork and about the same width of cortex, both varying in colour from dark reddish-brown to yellowish-grey. The main medullary rays are very wide in the outer part of the bast, but in the regular secondary bast they varied from one to three cells in width, and were very straight. In tangential sections the wider

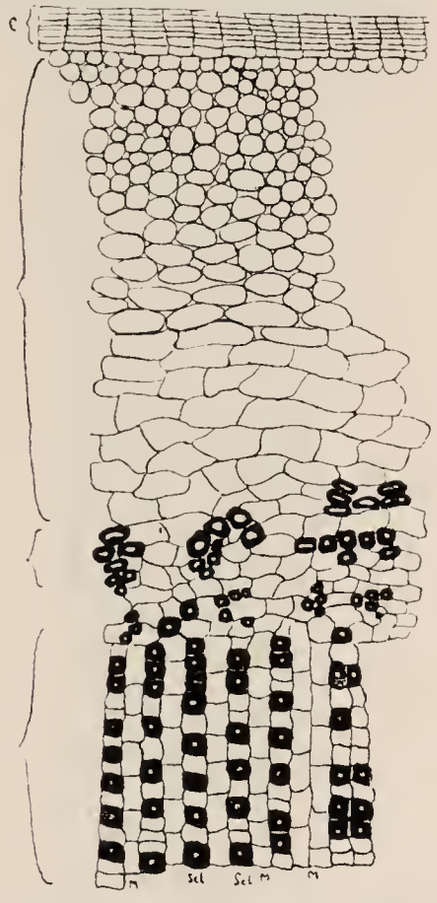

Fig. 1.—Young Bark of *P. Yohimba*; *c*, Cork; *co*, Cortex; *p*, Pericyclic Fibres; *b*, Bast; *m*, Medullary Rays; *scl.*, Sclerenchymatous Bast Fibres showing "beaded" effect.

Fig. 2.—Young Bark of *P macroceras*; *scl.*, Bast Fibres showing "twinning"; other lettering as in Fig. 1.

rays merge into narrow rays of larger cells at top and bottom, and thus acquire a somewhat rectangular appearance. Pericyclic fibres occur singly or in groups of two to three cells, but they are so scattered that they do not form so distinctive a feature of the old bark as of the young material, Fig. 1. The bast fibres are arranged in radial rows, usually one cell wide, and these fibres are frequently separated by single cells of bast parenchyma, giving a peculiar beaded effect to the rows. See Figs. 1, 3, and 4.

The bast fibres are spindle-shaped with pointed ends, not striated in section, and the lumen is usually punctiform, sometimes linear, very seldom slightly open. In addition to the beaded rows, bast fibres sometimes occur in rows of two to four cells with no intervening parenchyma, and less frequently

in rows which are two or three cells wide alternating with the narrow medullary rays. The arrangement of the fibres and the punctiform lumen are the only microscopic features which are at all characteristic of *P. Yohimba* as compared with *P. macroceras*.

Bark of Pausinystalia macroceras, K.Sch.

This type of bark has been found to be so closely similar to that of *P. Yohimba* that good diagnostic characters are very difficult to find. The macroscopic features are so similar that

Fig. 3.—Authentic (true) Bark of *P. Yohimba*.

Fig. 4.—Authentic (true) Bark of *P. Yohimba*.

with the small samples at first available no good distinguishing feature could be detected. The microscopic details are also very closely similar, but, since this bark was shown by Herzog[11] to contain much more of the inactive yohimbenine than of the active yohimbine, it is important that this false bark should be distinguished from the genuine yohimbe bark. Very careful consideration was, therefore, given to any features in which any difference at all was shown. The lumen of the pericyclic fibres in the younger herbarium material of *P. macroceras*, Fig. 2, is distinctly larger than in *P. Yohimba*, Fig. 1, and there are more of these fibres in the latter species, but in the older museum or commercial material the pericyclic fibres become so scattered and so difficult to distinguish from the bast fibres that these differences cease to be good diagnostic characters. It was observed, however, in the young bark that the bast fibres of *P. macroceras* very frequently occurred in

pairs side by side, and that this "twinning" was much rarer amongst the bast fibres of *P. Yohimba*. A careful examination of the museum specimens showed that both types were represented in the so-called authentic material. The history of the identification of these specimens indicated that, while the first two, Figs. 3, 4, which had relatively little twinning, were almost certainly authentic and genuine, the second two, Figs. 5, 6, might be false yohimbe bark of the *macroceras* type, since they had been identified with the first two on that similarity in macroscopic and microscopic characters which we now know occurs in both species. This identification was made

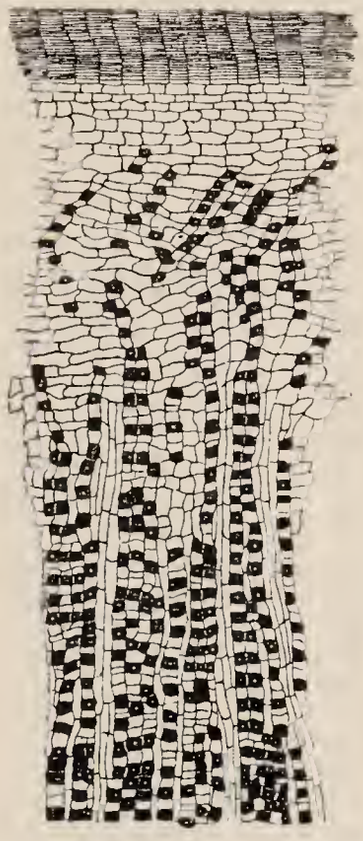

Fig. 5.—Old Bark of *P. macroceras*.

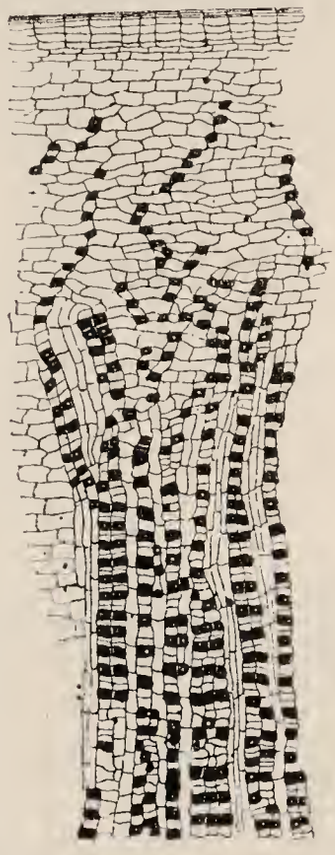

Fig. 6.—Old Bark of *P. macroceras*.

without the very careful comparison of the best material of the false and genuine barks, which has been necessary to distinguish the two types. It was, therefore, taken as more or less established that, while two of the museum specimens were genuine, two of them were false. *The twinning which can be used for diagnosis is that which occurs in the outer bast.* This conclusion was further corroborated by a slighter difference; in the *Yohimba* type most of the fibres have a punctiform lumen, while in the *macroceras* type linear lumens are commoner and punctiform lumens less frequent. Another characteristic of true yohimbe is the frequent occurrence of long chains of cells with the beaded effect mentioned above.

Since no further distinguishing feature could be detected in structure, the colour test with dilute sodium hydroxide solution, given by Weigel, was tried. The young barks of both species gave a reddish-brown colour, but when the scrapings were taken only from the inner surface of the old barks the samples indicated as genuine gave either a pure wine-red or a distinctly reddish tint, while the two suspected to be false gave a brown colour with only a slightly reddish tinge. This colour test is improved in many cases by using, instead of the

NaOH, five drops of 0·880 ammonia in 10 C.c. of water. The first two samples gave the same red tint, while the other two gave a fawn or light brown tint. The microscopic characters were thus supported by the colour tests, and it was rendered quite certain that two samples were false and two genuine.

We have, therefore, two or three diagnostic characters, each of which alone is open to objection in certain cases, but which, when taken together, afford fairly conclusive evidence. Taken in conjunction with the diagnostic characters described in the summary below, they may be described as quite conclusive.

Bark of Pausinystalia Talbotii, Wernh.

This recently-discovered species[31] occurs in Oban, Nigeria, and the bark of a small twig was examined microscopically. The

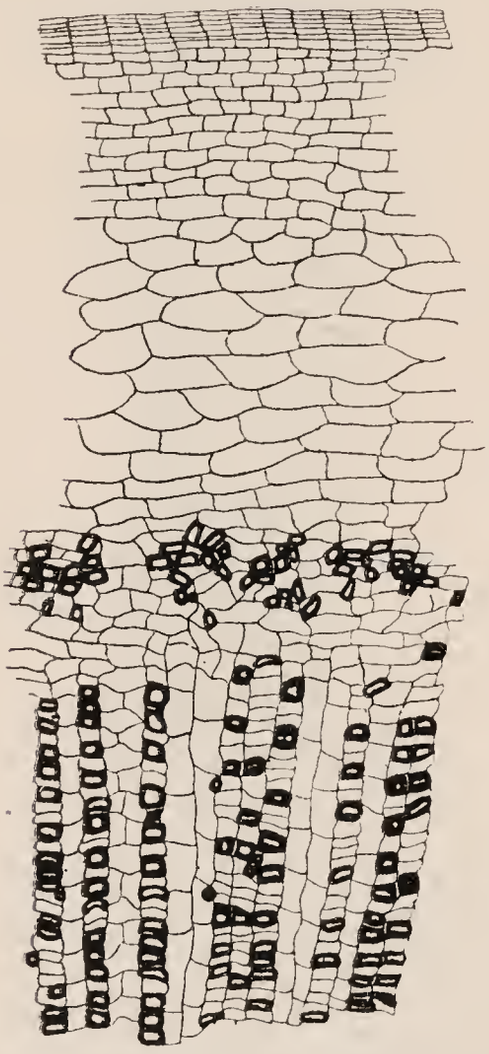

Fig. 7.—Transverse Section of Young Bark of *P. Talbotii*.

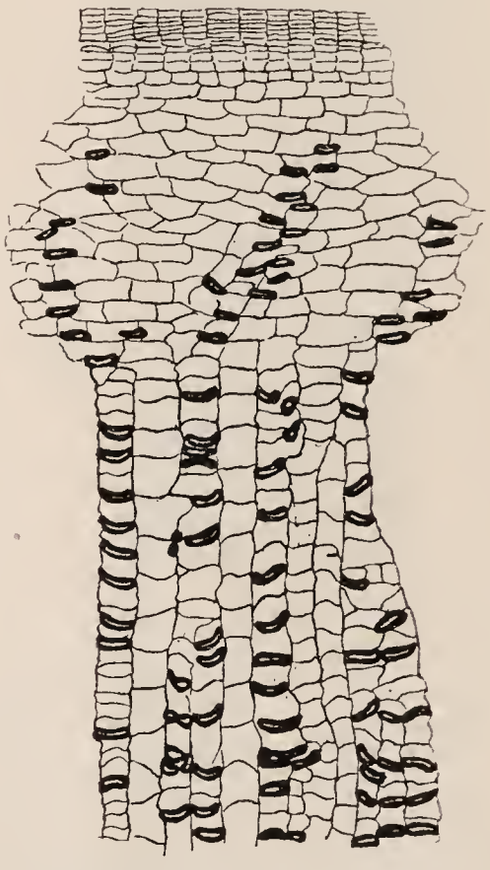

Fig. 8.—Transverse Section of Old Bark of *Corynanthe paniculata*.

arrangement of the bast fibres, Fig. 7, is similar to that in *P. Yohimba*, Fig. 1, but the species can be immediately distinguished by the lumen of the fibres, which is large and open, not punctiform or linear, as in *P. Yohimba*. There is no reason to suppose that *P. Talbotii* occurs in commerce at the present time.

Barks of the Corynanthe Species.

The barks of two species of this genus, *C. paniculata*, K. Sch. (= *Pseudocinchona africana*, A. Chevalier) and *C. Lane-Poolei*, were examined. These are readily distinguished from true yohimbe bark by the caustic soda or ammonia test; they give a

pale brown colour, with no trace of red. The first species is also distinguished by the large lumen of the bast fibres, which appear more or less collapsed, giving a linear lumen in the specimens examined (Fig. 8). *C. paniculata* is known to contain an alkaloid, corynanthine, said to be identical with yohimbine.

The second species, *C. Lane-Poolei*, is very similar to the *macroceras* type of *Pausinystalia*, from which it may be distinguished by the fewer fibres in the outer zone of the bast, and by the greater number of parenchymatous cells between the

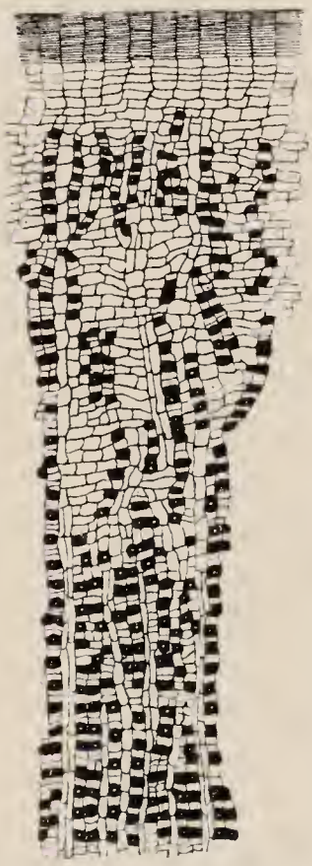

Fig. 9.—Transverse Section of Old Bark of *C. Lane-Poolei*.

Fig. 10.—Old Bark of Commerce resembling *C. Lane-Poolei*.

fibres in the one-cell wide radial rows of the secondary bast (Fig. 9). There seems some reason to suppose that this may form one of the so-called yohimbe barks of commerce, and it is at present undergoing expert chemical investigation. This type occurs as thicker channelled pieces or thin rolled quills; for characters see Schedule. One commercial sample, Fig. 10, resembles this species closely.

Commercial Samples.

Eleven commercial samples were examined in the first stage, with the result that five are considered to be genuine bark. These are identical in microscopical structure with *P. Yohimba*, and give the red or wine-red colour with caustic soda or ammonia when only the inner parts of the secondary bast are used. Three samples are considered to be false yohimbe bark of the *macroceras* type, since they show the "twinning" of the

bast fibres, especially in the outer bast, and give a brown or slightly reddish-brown colour with caustic soda, and a brown colour with ammonia. These barks also show two or three parenchymatous cells alternating with the bast fibres, instead of the regular chain-like alternation of true yohimbe bark.

One other sample, Fig. 11, is considered to be possibly the bark of *P. Trillesii*, since it occurred in French commerce and was found to bear a certain resemblance to Beille's figure of that species. The truncated arrangement of the outer bast bundles is the chief point of difference from *P. Yohimba*. This bark, however, responds to all three tests in the same way as *P.*

Fig. 11.—Commercial Bark possibly derived from *P. Trillesii*.

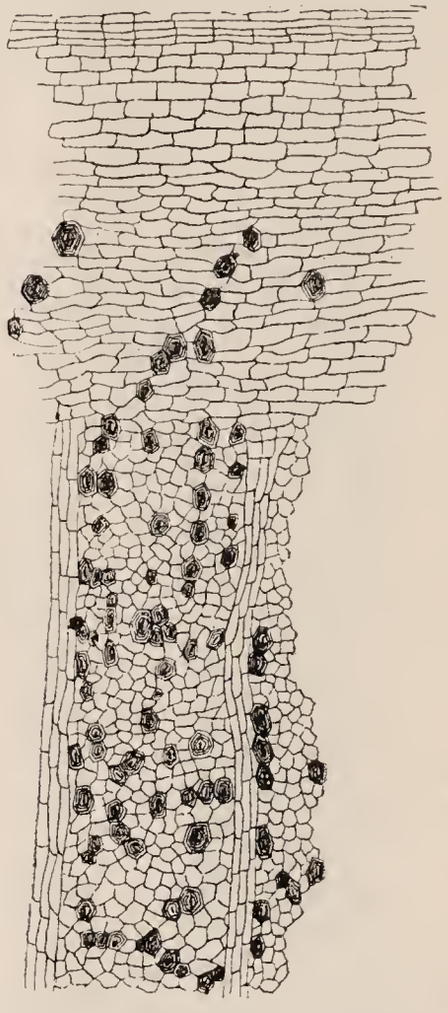

Fig. 12.—Commercial Bark, sold as Yohimbe Bark, source unidentified, but sample certainly not genuine.

Yohimba, and is known to have been imported into France from the Cameroons in 1914, not from Libreville in the French Congo, which is the only locality as yet for *P. Trillesii*.

One other commercial sample, Fig. 6, is regarded as very similar to, if not identical with, the bark of *Corynanthe Lane-Poolei*, and the value of that bark as a source of yohimbine remains in doubt pending the report from those at present investigating it.

This grouping of these ten commercial samples is regarded as provisional until the value of the diagnostic characters has been confirmed and supported by quantitative analysis of the alkaloidal contents.

The last sample, Fig. 12, is altogether different from any of the other barks examined. From the size of the bast

fibres, the scattered arrangement and smaller number of these cells, as well as the striated structure of their walls as seen in transverse section, it seems certain that this bark has not been derived from any species either of *Pausinystalia* or of *Corynanthe*. Without any doubt whatever, this sample can be described as not genuine.

Sources of Material.

Acknowledgments are due to the Keeper of the Department of Botany, British Museum, for the three herbarium specimens; to the Director of the Imperial Institute for certain of the museum specimens, and for those of *C. Lane-Poolei*.

Acknowledgments are also due to E. M. Holmes, Esq., F.L.S., for the rest of the specimens, and we take this opportunity of thanking him for suggesting this work and supplying so much of the material.

Supplementary Investigation.

There was still a certain degree of uncertainty about the value of the diagnostic tests described above when, by the kindness of the importing merchants, Messrs. W. D. Woodin and Company, of Liverpool, two dozen large pieces of bark became available. These were in seven packages, labelled H1. H2. H3. W1. W2, W3. W4.

After the microscopic structure of each piece had been investigated, the diagnosis by that means was checked and rechecked with the caustic soda and ammonia tests until all three tests coincided. The results were as follows:—H1, H3, W1, W2, W3—all genuine; in H2 one piece was genuine and three were false; in W4 one piece was genuine and four were false; making a total of seven pieces false out of twenty-four. When the barks had been separated on these lines it became apparent that they could be distinguished with a reasonable degree of certainty by the naked eye.

As the result of the examination of this material we can now give the following summary of the distinguishing characters of the *Yohimba* and the *macroceras* types of bark.

Summary.

Genuine yohimbe bark, derived from *Pausinystalia Yohimba*, usually occurs in channelled pieces, 4 to 10 Mm. thick; with a varying tinge of red in the grey-brown or brown outer and inner surfaces; the outer surface is longitudinally furrowed, the edges of the furrows scarcely or not at all raised above the general level of the surface; numerous narrow transverse cracks occur on the outer surface at fairly regular intervals of 1-2 Cm.; the cork adheres closely. Occasionally this type of bark is derived from very old tree trunks, and is then dark red on the inner and cut surfaces; 15-20 Mm. thick; with a scaly outer bark showing few or no transverse cracks. Occasionally also this type of bark seems to be derived from branches rather than from the trunk of the tree, and is then much thinner, 2-3 Mm. thick; while the transverse cracks are very narrow, shallow, and inconspicuous, but still present to careful inspection.

Transverse sections under the microscope show a characteristic "beaded" alternation of bast fibres with parenchymatous cells, and also show little or no "twinning" of the bast fibres, especially in the outer zone of the bast where the rows are fewer. A few scrapings from the *inner* surface of the secondary bast, when shaken with dilute caustic soda solution (ten drops of a solution of NaOH. sp. gr. 1·168, in 30 C.c. of

water) give a red colour, varying in different samples from wine-red to distinctly reddish-brown. Treated in the same way with dilute ammonia (five drops of 0·880 solution in 10 C.c. of water) the same colours are developed; this ammonia test is usually more distinctive, but the colour may take longer to develop.

False yohimbe bark, derived from *Pausinystalia macroceras*, usually occurs in channelled, or flattened and severely scraped pieces; 4 to 15 Mm. thick; with little or no red tinge; usually with a dark brown outer surface, showing *when unscraped* characteristic longitudinal furrows, the edges of which are puckered so that they stand up as rounded ridges above the general level of the surface; transverse cracks when they occur are few and very irregularly spaced; the cork frequently exfoliates easily. Transverse sections under the microscope show little or no "beading" in the radial rows of bast fibres, but do show "twinning" of these fibres; this feature, when it extends to the outer bast, is a good diagnostic character. A few scrapings from the inner surface, treated with caustic soda or ammonia as described above, give a brown colour, with, in some samples and with caustic soda, a faint tinge of red.

We desire to express our gratitude to Messrs. W. D. Woodin and Co. for their kindness in making it possible to arrive at a more or less definite conclusion as to the distinctive features of the genuine yohimbe bark.

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